IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants:	Kai-Uwe Lewandrowski and Debra J. Trantolo		
Serial No.:	10/054,171	Art Unit:	1617
Filed:	January 17, 2002	Examiner:	Gina C. Yu
For:	*METHODS OF DIAGNOSIS AND TREATMENT OF OPSTEOPOROSIS*		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF TO EXAMINER'S ANSWER

Sir:

This is a reply brief to the Examiner's Answer mailed January 8, 2007, in the above-referenced application

It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 7, 9, and 15-18 are free of the prior art and would be allowable if rewritten in independent form.

The issues now present on appeal are:

(i) whether claims 1, 2, 12 and 13 are enabled as required under 35 U.S.C. § 112, first paragraph. Appellants appreciate the withdrawal by the Examiner of the rejection of claims 3-11 and 14-19 under 35 U.S.C. § 112, first paragraph.

(ii) whether claims 1-6, 8, 10 and 11 are non-obvious under 35 U.S.C. § 103(a) over WO 00/13024 to Findlay ("Findlay") in view of Nair, et al., "Molecular Chaperones Stimulate Bone Resorption", *Calcified Tissue International*, 64:214-218 (1999) ("Nair"); and

(iii) whether claims 1, 10, 12-14 and 19 are non-obvious under 35 U.S.C. § 103(a) over Findlay in view of Reddi, et al., "The *Escherichia coli* Chaperonin 60 (groEL) is a Potent Stimulator of Osteoclast Formation", *Journal of Bone and Mineral Research*, 13(8):1260-1266 (1998) ("Reddi").

(2) ARGUMENT

Appellants affirm all of the arguments made in the Appeal Brief.

(a) Rejection under 35 U.S.C. § 112, first paragraph, enablement

The Examiner has withdrawn the rejection of claims 3-11 and 14-19 under 35 U.S.C. § 112, first paragraph. Claims 1, 2, 12 and 13 remain rejected as allegedly not enabled as required by 35 U.S.C. § 112, first paragraph, on the basis that "while being enabling for detection of osteoporosis caused by bacterial infection, does not reasonably provide enablement for detecting osteoporosis by measuring concentrations of other types of pathogens such as viruses, viral produced factors, protozoa, protozoal produced factors, parasites, parasitic produced factors, fungi and fungal produced factors".

All of claims 1, 2, 12 and 13, relate to detection of a marker associated with an infectious agent, a factor produced by an infectious agent, or a heat shock protein (which is endogenous to cells and tissue, but whose expression is altered upon infection with an infectious agent) as a means of detecting osteoporosis.

The Examiner has not established on the record a reasonable basis for questioning the adequacy of the disclosure to enable a person of ordinary skill in the art to make and use the claimed invention without resorting to undue experimentation

The Examiner has presented no arguments on the record that the claims are not enabled for detecting osteoporosis using heat shock proteins produced in response to an infectious agent as a marker. The Examiner has also agreed that the claims are enabled for detecting osteoporosis where bacteria are detected.

The basis for the rejection for lack of enablement is that the Examiner apparently believes one can make and use the claimed method, but not for infectious agents other than bacteria or factors produced from infectious agents other than bacteria.

It is well established that a specification is presumed to be enabling. A *prima facie* case of non-enablement can only be made upon a showing of evidence, ***not argument,*** of why one skilled in the art would not be able to make and use the claimed subject matter. The Examiner has provided nothing in support of this rejection other than ***her assertions*** and by reference to Nair on the basis that Nair states that not all bacterial molecular chaperones stimulate bone resorption. The Examiner's use of this reference as evidence to question the adequacy of the disclosure to enable the claims is flawed for at least the reasons presented below.

First, contrary to the assertion by the Examiner, Nair teaches that all bacterial molecular chaperones stimulate bone resorption. In fact, as can be seen in Figures 1 and 2, ***all bacterial HSPs*** tested had a similar ability to stimulate calcium release from murine calvarial bone. The

authors conclude that *murine* hsp 47 does not have activity in this assay (this conclusion is unsupported by the data; see below). However, murine hsp 47 is *not* a factor produced by an *infectious agent*, and therefore any conclusions drawn from data using this factor have no bearing on the enablement of the claims.

Second, although the authors conclude in the abstract and in the last paragraph of page 217 that murine hsp 47 does not induce murine calvarial bone resorption, the data in Figure 3 do not support this conclusion. Addition of the lowest tested concentration of hsp 47 (0.1 μg/ml) to the assay significantly increased the release of calcium by approximately 3- to 4-fold. Although higher amounts of hsp 47 did not cause a further increase in calcium release, these concentrations still stimulated calcium release approximately 2-3 times higher than control. The reason for the lack of dose dependency for hsp 47 in this assay is not clear, although it could be due to any number of factors, such as saturation or desensitization of receptors, or the fact that the hsp 47 used in the assay was of murine origin, as opposed to the other tested mammalian HSPs, which were either of human (hsp 27 and hsp 90) or bovine (hsp 70) origin (page 214, right column). Although it is not clear why the effect of hsp 47 in this assay was not dose dependent, it is clear that hsp 47 stimulated significant calcium release in this assay, especially at lower concentrations which are more likely to reflect actual *in vivo* concentrations.

Further, this reference only presents evidence of the ability of various bacterial and mammalian HSPs to stimulate calcium release from murine calvaria in an *in vitro* assay. Even if one concludes from Nair that murine hsp 47 (which is *not* a factor produced by an infectious agent) does not stimulate release of calcium in an *in vitro* murine calvaria assay (a conclusion that is *not* supported by the data), this assay is insufficient to demonstrate that this factor does not contribute to osteoporosis. The specification defines osteoporosis as a systemic disorder characterized by decreased bone mass and microarchitectural deterioration of bone leading to

bone fragility and increased susceptibility to fractures of hip, spine and wrist (page 1, lines 18-21). The specification also discloses, using bacteria as an example, that infectious agents could promote pathological bone loss by at least three different mechanisms: 1) direct destruction of the non-cellular components of bone by liberating acid and proteases, 2) promotion of cellular processes that stimulate the degradation of bone and 3) inhibition of the synthesis of bone matrix (page 15, lines 3-7). The specification further discloses that mechanism 2 and 3 may be either a direct effect of components released by infectious agents or a consequence of the induction of host factors, for example, cytokines or prostaglandins that then act on bone cells (page 15, lines 7-10). The specification discloses a number of factors released by infectious agents that inhibit bone formation through their effects on the cell cycle and proliferation. The *in vitro* assay used in Nair is insufficient to test mechanisms 2 and 3. Removing the calvarial bone from the mouse isolates the bone from the other tissues and organs of the host and thus this assay system does not detect an effect of a factor released by an infectious agent on bone which functions through regulation of host factors. This assay system is also insufficient to test mechanism 3 because an effect of a factor on bone density resulting from a decrease in the synthesis of bone matrix would not be detected over the short (48 hour) time period of the assay. Thus, this *in vitro* assay system is significantly limited in its ability to test for the effects of factors on bone pathology and possible effects of factors on bone *in vivo* cannot be ruled out.

Finally, Nair provides no evidence that one skilled in the art would not extrapolate from bacteria to other infectious agents. In contrast, Appellants have described the known association of certain parasites and protozoans with bone disease (See page 34) and the association of a number of viruses with production of HSPs (pages 39-40; 31-32).

A proper analysis of the Wands factors demonstrates that claims 1, 2, 12 and 13 are enabled

While Appellants maintain that the Examiner has not met the initial burden of setting forth a reasonable explanation as to why the claims of the present application are not enabled, an analysis of the Wands factors clearly demonstrates that claims 1, 2, 12 and 13 are enabled by the specification of the present application.

Claim 1 defines a method of detecting osteoporosis in a individual to be tested by (1) obtaining a sample of bone-related tissue or cells. (2) assaying the concentration of a marker selected from the group of infectious agents, factors produced by infectious agents, and heat shock proteins produced in response to an infectious agent, and (3) comparing the concentration of the at least one marker with the concentration of the marker in a sample of the same bone related tissue or cells from a control individual who does not have osteoporosis.

Methods of obtaining a sample of bone related tissue or cells from an individual are well known in the art. Methods of assaying the concentration of a marker are also well known in the art and are disclosed in the specification at least at page 8, lines 4-29, and at page 9, lines 1-12. Methods of comparing the concentration of a marker from an individual with the concentration of said marker from a control individual are well known in the art and are disclosed in the specification at least at page 11, lines 21-28, and at page 19, lines 19-21. Furthermore, ***the Examiner admits in the office action mailed July 1, 2004 at page 3 lines, 15-17 and in the advisory action on page 2, that general methods for obtaining a sample of bone related tissue or cells from an individual; of assaying the concentration of infectious agents or factors produced by infectious agents or heat shock proteins produced in response to infectious agents; and of comparing the concentration of a marker from an individual to a control individual are well known in the art.*** This is all that is required to practice the method of

detecting osteoporosis as defined by the claims of the present application. While measurement of these factors may require experimentation, one of skill in the art typically engages in such experimentation.

It is clear from the discussion above that the quantity of experimentation to perform the method as defined by the claims is minimal, that the skill of one in the art is high and that the specification provides sufficient guidance for one of skill in the art to perform the method as defined by the claims. It would not require undue experimentation to perform the method for detecting osteoporosis as defined by the claims 1, 2, 12 and 13. Therefore, claims 1, 2, 12 and 13 are enabled by the specification.

(b) Rejections Under 35 U.S.C. § 103(a)

Claims 1-6, 8 and 11 were rejected under 35 U.S.C. § 103(a) as obvious over Findlay in combination with Nair. Claims 1, 12-14, and 19 were rejected under 35 U.S.C. § 103(a) as obvious over Findlay in combination with Reddi. The Examiner stated in the Examiner's Answer that claim 10 was inadvertently omitted in the rejection made under 35 U.S.C. § 103(a) as obvious over Findlay, apparently in view of Nair but possibly also over Reddi.

Claims 7, 9, and 15-18 have not been rejected over the prior art. These claims differ from the rejected claims as specific to HSP60 (claim 7), ubiquitin (claim 9), wherein the agent to be detected is a bacterially produced factor: endotoxin-LPS, gapstatin, and dermonecrotic toxin (claims 15-18).

1. Rejection of claims 1-6, 8, 10 and 11 over Findlay in view of Nair

Findlay

Findlay discloses a method of measuring **internal** regulators of bone remodeling as a predictive measure for the **potential** onset of certain skeletal disorders. Findlay discloses a method that includes the steps of taking a sample of body tissue or body fluid and measuring or

estimating the level of a regulator of bone remodeling. Findlay discloses internal regulators of bone growth such as growth factors, cytokines, and associated proteins.

Findlay does not recognize a critical element of the claimed method: the discovery of an association between the development of osteoporosis and infectious agents.

Findlay does not disclose any heat shock proteins as defined specifically by claims 3, 4, 10, and 11.

Nair

Nair does not make up for the deficiency of Findlay. Nair measures the activity of molecular chaperones in an *in vitro* murine calvarial bone resorption assay. Nair recognizes that certain bacterial and mammalian molecular chaperones can stimulate bone resorption. Nair does not make the connection however, that one could screen for osteoporosis by detecting infectious agents, factors produced by infectious agents, or HSPs in one individual and comparing it with the levels in another.

The combination of Findlay and Nair

No where is there any suggestion in either reference of a screen for osteoporosis based on an ***external stimulus for the disease***. Findlay is looking at endogenous causes of osteoporosis. Nair is looking at bone resorption in an *in vitro* assay by measurements of molecular chaperones.

Nowhere is there any teaching that would motivate one of skill in the art to move from Findlay, which teaches away from an external cause of osteoporosis, to Nair, which relates to an *in vitro* bone resorption assay, not osteoporosis, and arrive at the claimed method, much less with any reasonable expectation of success.

Findlay and Nair do not disclose each and every element of the claims as defined in the present application. Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest

the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). Findlay and Nair do not disclose or suggest a method of detecting osteoporosis in an individual that contains the steps of measuring an infectious agent such as bacteria, or a factor produced by an infectious agent, or **endogenous** factors that are altered in expression **due to infection**. Findlay and Nair certainly do not disclose or suggest measuring endogenous factors, such as heat shock proteins, that are **induced by infection** to detect osteoporosis in an individual. The Examiner has not pointed to a single place in Findlay or Nair that provides support for each of the elements of the claims as defined by the present application. The Examiner simply argues that the claims are obvious because Findlay describes an assay that measures **internal** regulators of bone remodeling and Nair states that molecular chaperonins can stimulate bone resorption. It is clear that Findlay and Nair do not disclose each and every element of claims 1-19 of the present application.

In addition to disclosing each of the claimed elements, there must be some suggestion to modify or combine the reference teachings. One or ordinary skill in the art would not combine Findlay with Nair because neither reference provides the modifications that would bring the references into conformity with the claims of the present application. Furthermore, Findlay and Nair do not provide any motivation for one of skill in the art to combine these references. The Examiner has failed to identify a single place in Findlay or Nair that provides one of skill in the art with the motivation to combine these references.

Finally, Findlay and Nair do not provide one of ordinary skill in the art with a reasonable expectation of success. Findlay and Nair do not disclose, suggest or provide one of ordinary skill in the art with a reasonable expectation of success that assaying the concentration of an infectious agents, or a factor produced by an infectious agent, or **endogenous** factors that are

altered in expression **due to an infectious agent** in bone related tissue or cells can be used to detect osteoporosis. Again, the Examiner has not provided any evidence of a reasonable expectation of success.

It is clear that to establish a *prima facie* case of obviousness the cited references must (1) recite each and every element of the claims, (2) provide one of skill in the art with the motivation to combine the cited references and (3) provide one of ordinary skill in the art with a reasonable expectation of success. The Examiner has not established a *prima facie* case of obviousness because the Examiner has not provided a reasonable expectation of success and has not provided the motivation to combine the cited references. While the Examiner argues that Findlay and Nair disclose each and every element of the claims of the present application, it is clear from the discussion above that they do not. Even considering that the Examiner has established a *prima facie* case of obviousness, the claims are still not obvious because Findlay and Nair do not disclose each and every element of the claims, do not provide a motivation to combine and do not provide a reasonable expectation of success. Therefore, claims 1-6, 8, 10 and 11 are not obvious over Findlay in view of Nair.

2. **Rejection of claims 1, 10, 12-14 and 19 over Findlay in view of Reddi**

Findlay

As discussed above, Findlay discloses a method for a predictive assay that measures **internal** regulators of bone remodeling such as growth factors and cytokines as a predictive measure for the **potential** onset of certain skeletal disorders.

Reddi

Reddi states that cpn60 (groEL) from *E. coli* stimulates bone resorption and osteoclast formation in culture. Reddi also states that a protein on the surface of *Actinobacilus actinomycetemcomitans*, which causes periodontal disease, can stimulate bone resorption.

Reddi does not relate to osteoporosis. At most, Reddi shows that direct application of a HSP from a bacteria to the surface of bone allegedly can cause osteoclast mediated pit formation in the surface of the bone. Osteoporosis is not caused by direct application of a factor to bone cells, however, but is a decrease in bone density ***within*** the bone. One skilled in the art would not be able to extrapolate from studies relating to periodontal disease, which is totally different from osteoporosis, to osteoporosis. Even Reddi acknowledges that his studies are distinct from studies involving osteoporosis, noting in the abstract "Whether endogenous ("self") chaperonins have a role in other bone loss disorders, such as osteoporosis, is an intriguing possibility". The authors certainly do not indicate that they would consider the results predictive of any other bone disorder; therefore neither should the Examiner.

The combination of Findlay and Reddi

As discussed above, Findlay does not lead one of skill in the art to a method for detecting osteoporosis since Findlay does not recognize that infectious agents, directly or indirectly, can lead to osteoporosis. Findlay relates solely to endogenous (i.e., mammalian) HSPs. Reddi does not make up for this deficiency. Reddi relates to periodontal disease and looks at surface pit formation mediated by osteoclasts; not alteration in bone density within the bone.

Findlay and Reddi do not disclose or suggest a method of detecting osteoporosis in an individual that contains the steps of measuring an infectious agent such as bacteria, or a factor produced by an infectious agent, or endogenous factors that are altered in expression due to infection. Reddi certainly does not disclose or suggest assaying endogenous heat shock proteins that are altered in expression due to an infectious agent. There is no teaching that would lead one of skill in the art to modify Findlay to measure infectious agents, or products thereof, instead of endogenous HSPs, with a reasonable expectation of success. Reddi does not even mention mammalian heat shock proteins in connection with bone resorption. It is clear that Findlay and

Reddi do not disclose each and every element of the claims of the present application. Furthermore, Findlay and Reddi do not provide any motivation for one of skill in the art to combine these references. One of ordinary skill in the art would not be motivated to combine Findlay and Reddi because they do not disclose each and every element of the claims.

The Examiner has again failed to establish a *prima facie* case of obviousness. The examiner has not identified a single place in Findlay or Reddi that provides one of skill in the art with the motivation to combine these references as appellants have done. Findlay and Nair do not disclose, suggest or provide one of ordinary skill in the art with a reasonable expectation of success that assaying the concentration of an infectious agents, or a factor produced by an infectious agent, or **endogenous** factors that are altered in expression **due to an infectious agent** in bone related tissue or cells can be used to detect osteoporosis.

Therefore, claims 1, 12-14 and 19 are not obvious over Findlay in view of Reddi.

(3) SUMMARY AND CONCLUSION

(i) The Examiner has not met the initial burden of setting forth a reasonable explanation as to why the claims of the present application are not enabled. A *prima facie* case of non-enablement can only be made upon a showing of evidence, not argument, of why one skilled in the art would not be able to make and use the claimed subject matter. The only evidence presented by the Examiner in this regard fails to adequately support an argument of non-enablement. Further, as admitted by the Examiner, claims based on measurement of bacteria, bacterial induced proteins, and HSPs are enabled. The Examiner has not provided any reason one skilled in the art would not also have a reasonable expectation of success based on other etiological agents such as parasites or protozoa based on the data provided in the application. Methods for obtaining a sample of bone related tissue or cells from an individual; of assaying the concentration of infectious agents or factors produced by infectious agents or heat

shock proteins produced in response to infectious agents; and of comparing the concentration of a marker from an individual to a control individual are well known in the art. Therefore, it would not require undue experimentation to perform the method for detecting osteoporosis in an individual as defined by claims 1, 2, 12 and 13 of the present application.

(ii) The Examiner has not established a *prima facie* case of obviousness because the Examiner has not provided a reasonable expectation of success and has not provided the motivation to combine the cited references. While the Examiner argues that Findlay and Nair or Findlay and Reddi disclose each and every element of the claims of the present application, it is clear from the discussion above that they do not. Findlay discloses a method of measuring **internal** regulators of bone remodeling. Nair discloses that mammalian and bacterial molecular chaperones can stimulate bone resorption; not be predictive of osteoporosis. Reddi discloses that bacterial molecular chaperones can stimulate bone resorption. Findlay, Reddi, and Nair alone or in combination do not lead one of ordinary skill in the art to a method of detecting osteoporosis in an individual that contains the steps of measuring an infectious agent such as bacteria, or a factor produced by an infectious agent, or endogenous factors that are altered in expression due to infection, as defined by the claims of the present application, with a reasonable expectation of success.

Allowance of claims 1-6, 8, 10-14 and 19 is respectfully solicited.

Respectfully submitted,

/ Patrea L. Pabst /

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